Hemangioblastoma and Von Hippel–Lindau Disease

16

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Contents

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16.1 Hemangioblastoma

Hemangioblastoma (HB) is an infrequent, benign (WHO grade I), highly vascular, well-demarcated, slowly growing, solid, or cystic neoplasm of unspecified cellular origin [1]. It is confined to the central nervous system (CNS), the brain, spinal cord, and retina, rarely occurring in the nerve roots or peripheral nerves. HB accounts for about 10% of tumors of the posterior fossa, the site of its predilection, but only about 2% of all intracranial tumors. HB of the retina [1, 14, 19], originating from the inner mid-peripheral retina, is histologically identical to HB elsewhere in the CNS. Some 20% of HBs (up to 50% of retinal HBs) may be associated with Von Hippel–Lindau disease (VHL), but estimates are inaccurate because not all patients are screened for the mutations and other manifestations of VHL [1, 6, 10, 15, 20]. VHL-related HBs occur at 20–30 years of age and sporadic ones at 40–50 years.

16.2 Von Hippel–Lindau Disease

Von Hippel–Lindau disease (VHL) is a rare autosomal dominant tumor syndrome, estimated to occur in 1 of 36,000 live births [1] (see also GeneReviews at www.genetests.org). VHL is caused by a germline mutation or deletion in one allele of the VHL tumor suppressor gene (OMIM 608537) with a coding sequence of three exons on chromosome 3p25–26 [1, 6]. Somatic inactivation of the other VHL allele results in tumor formation in the VHL target organs, typically multiple tumors at an earlier age than in sporadic cases: HB of the CNS and retina, clear cell renal cell carcinoma (RCC), pheochromocytoma, neuroendocrine tumor and microcystic adenoma of the pancreas, and endolymphatic sac tumor

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of the inner ear. In addition, VHL predisposes to multiple visceral cysts, including those of the kidneys, liver, and pancreas. About 80% of the VHL cases are familial, and 20% are caused by new mutations. Almost all carriers of a mutant *VHL* allele will develop manifestations of VHL by 65 years of age, and so their children have a 50% risk of getting the dominantly inherited disease. The VHL phenotype is highly variable. VHL families are divided according to the absence (type 1) or presence (type 2) of pheochromocytoma [2]. Most type 1 families have truncating mutations or missense mutations predicted to disrupt the folding of the VHL protein, whereas most type 2 families are affected by missense mutations. Type 2 families are further subdivided according to the absence (type 2A) or presence (type 2B) of RCC, or carrying pheochromocytomas only (type 2C). VHL clearly reduces the length of life, with a mean age of 40–50 years at death, which is mainly caused by RCCs and HBs of the CNS [1].

16.3 VHL Protein

HB is obviously caused by functional inactivation of the *VHL* gene and the VHL protein (pVHL), but the exact mechanisms of tumorigenesis and possible role of other genes have not been elucidated [1, 8]. pVHL is widely expressed, also in organs not developing VHL manifestations. *VHL* −/− mice die in utero because of vascular abnormalities of the placenta, while *VHL* −/+ ones appear phenotypically normal. pVHL has multiple functions, e.g., in the regulation of angiogenesis and the cell cycle, with multiple signaling pathways involved. As to the vascular nature of VHL-related tumors, pVHL significantly interacts with the hypoxia inducible factor 1 (HIF-1). The α-domain of pVHL forms a complex with elongin B, elongin C, cullin-2, and Rbx1, and this complex exhibits E3 ubiquitin ligase activity towards the α-subunit of HIF-1 (HIF-1 α). In normoxic cells, the β-domain of pVHL is able to bind HIF-1α for ubiquitin-mediated degradation. In pVHL-deficient cells, the HIF-1α and HIF-1β accumulate, resulting in elevated transcription of a variety of HIF-controlled genes, including the vascular endothelial growth factor (VEGF) gene. HB tissue expresses VEGF and its receptors as well as other angiogenic factors that apparently play a prominent role in its development. HB tissue may produce erythropoietin, also detectable in the cyst fluid, possibly due to a dysregulated function of HIF-1α.

16.4 Symptoms and Clinical Signs

16.4.1 Hemangioblastoma

Most sporadic HBs are single lesions occurring in the cerebellum (Figs. 16.1 and 16.2) or the brain stem, occasionally in the spinal cord (Fig. 16.3), and rarely in the

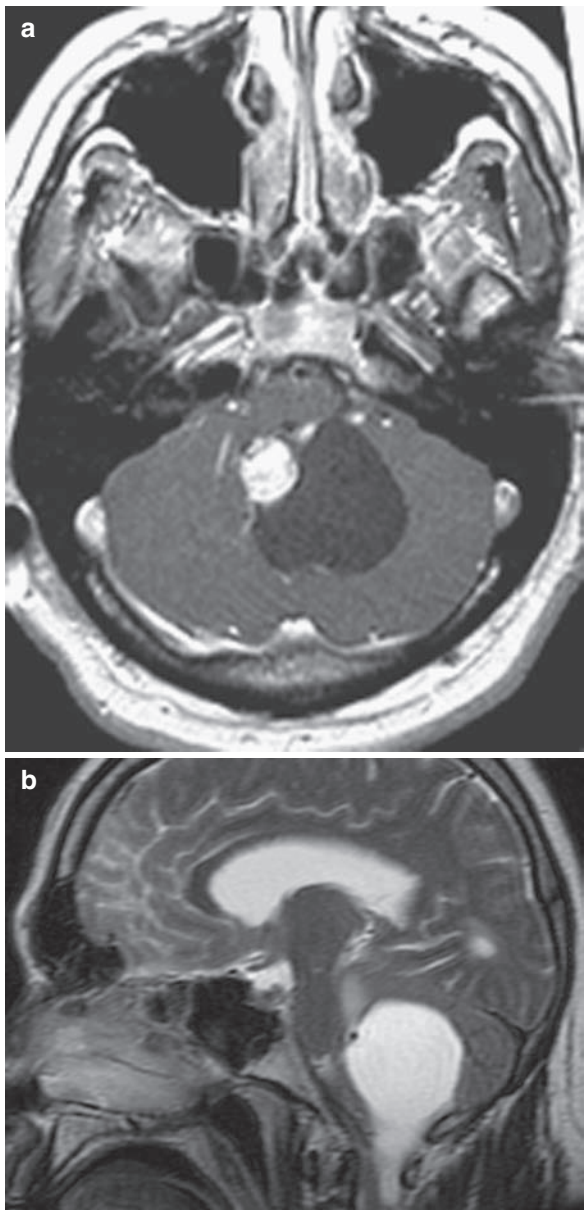

Fig. 16.1 Cystic hemangioblastoma of the cerebellum. MRI with an axial T1 image with contrast enhancement (**a**) and a sagittal T2 image (**b**)

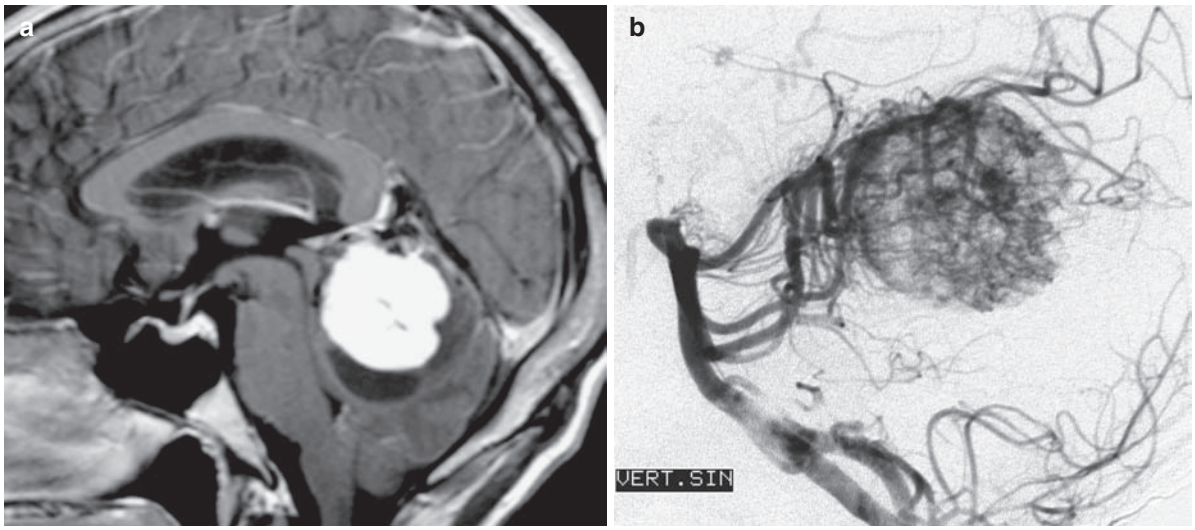

Fig. 16.2 Large recurrent hemangioblastoma of the posterior fossa. MRI (**a**) and angiography (**b**)

cerebrum [1, 15]. They often produce an adjoining cyst (Fig. 16.1) or a syrinx in the spinal cord (Fig. 16.3). In the posterior fossa, the fourth ventricle may become compressed, causing hydrocephalus with symptoms and signs of increased intracranial pressure. Focal symptoms include ataxia, dysmetria, tremor, unstable gait, and vertigo. Patients may also present with polycythemia and increased hematocrit in blood tests due to erythropoietin secretion of HB tissue. In the spinal cord, HBs may present with pain, spasticity, weakness, sensory changes, hyperactive reflexes, and impaired urination because of the solid tumor and/or the syrinx. Only rarely, HBs manifest by bleeding into the adjacent brain or spinal cord, or into the subarachnoid space [5].

16.4.2 Hemangioblastoma of the Retina

HB of the retina can be asymptomatic for years [1, 14, 19]. Usually, visual symptoms such as flashing and floaters occur, and there is progressive visual impairment due to leakage from incompetent capillary walls of HB tissue. This leads to secondary changes in the vitreous and retina, such as premature posterior vitreous detachment, retinal break, vitreous hemorrhage, lipid exudates and edema in the macula, or preretinal fibrosis. In large HBs, total retinal detachment may occur either due to accumulation of fluid between the photoreceptor layer and the retinal pigment epithelium, or by vitreous traction caused by vitreous strands and epiretinal membranes and/or retinal breaks.

16.4.3 Von Hippel–Lindau Disease

In VHL, HBs are typically multiple, occurring as incipient or symptomatic lesions in different sizes and combinations in the cerebellum, brain stem, spinal cord, and retina, depending on the severity, progression, and stage of the disease [1, 15]. HB of the retina is the first manifestation in half of the VHL patients, at the average age of 25 years, and it is usually bilateral and multifocal, or becomes so over the years [1, 14, 19]. RCC develops in about 40% of VHL patients, at the average age of 35 years, often as multifocal lesions in association with cysts in both kidneys, but showing lower grade histology than the sporadic form of RCC [1, 4, 16, 19]. Pheochromocytoma, a catecholamine-producing tumor of the adrenal medulla and ectopic locations, occurs in 20–35% of VHL patients at the average age of 30 years, often as bilateral and multiple lesions but rarely malignant [1, 6, 10, 12]. Neuroendocrine tumors and microcystic adenomas of the pancreas may occur, but rarely carcinomas. Endolymphatic sac tumors in the petrous bone in the region of the vestibular aqueduct cause tinnitus, hearing loss, and vertigo. VHL also predisposes to multiple cysts in the kidneys, pancreas, and liver, and they require follow-up because of possible adjoining malignancy.

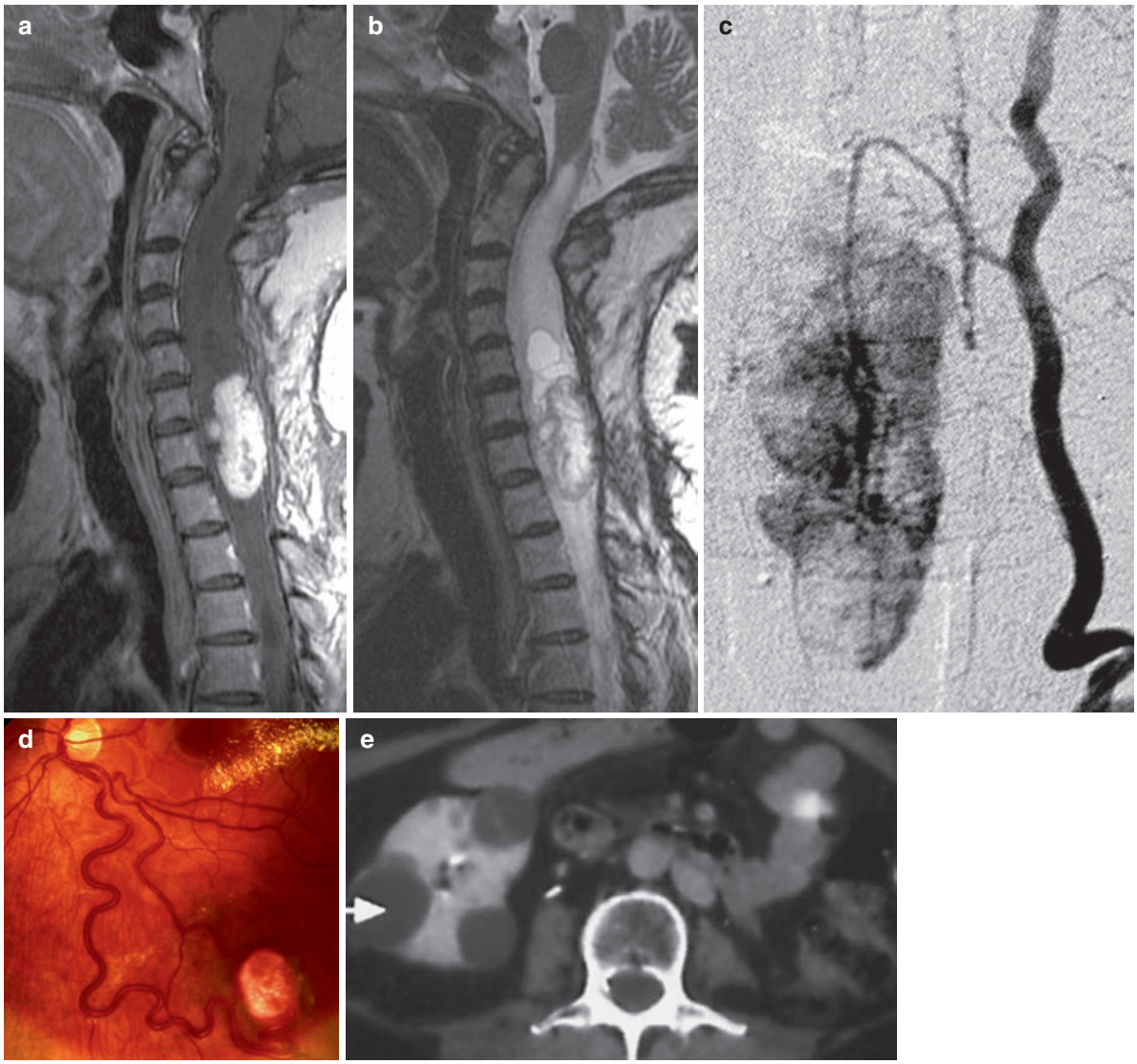

Fig. 16.3 Von Hippel–Lindau disease. Large spinal hemangioblastoma with contrast enhancement in a sagittal T1 image (**a**) and with adjacent syrinx in a T2 image (**b**). Angiography showing a prominent feeding artery from the vertebral artery (**c**). Retinal hemangioblastoma (*lower right*) with strong feeding vessels (**d**). Bilateral renal cell carcinoma: the right kidney with cysts (*arrow*), the left kidney removed (**e**)

16.5 Diagnostics

16.5.1 Synopsis

HB of the retina is an ophthalmological diagnosis, and HBs elsewhere in the CNS are imaged by MRI [10], sometimes supported by digital catheter angiography. Patients with HB should undergo exclusion of VHL by the following: family history; contrast-enhanced MRI of the brain, the spinal cord, and the organs of the abdominal cavity; retinal microscopy by an ophthalmologist. Mutation analysis may also be considered [20].

16.5.2 Histopathology of Hemangioblastoma

Histologically, HB tissue is composed of stromal cells, the neoplastic cells of still undefined origin, as well as endothelial cells, pericytes, and mast cells [1]. HB

tissue is characterized by large vacuolated stromal cells and a rich capillary network. The "clear cell" morphology due to lipid-containing vacuoles in stromal cells may suggest metastatic RCC, but in immunostaining HB is negative for cytokeratin, epithelial membrane antigen (EMA), and pan-epithelial antigen. The cell proliferation rate is low, with the Ki67 index less than 1% [1]. HB of the retina is histologically identical to HB elsewhere in the CNS. HB tissue is able to produce, by unknown mechanisms, intratumoral and paratumoral cysts with no actively secreting capsule. HB tissue may secrete erythropoietin, detectable in the cyst fluid, an obvious cause for polycythemia and increased hematocrit in blood tests.

16.5.3 Imaging of Hemangioblastoma

MRI shows HB as an intensively enhanced, well-circumscribed, possibly nodular, either homogeneous or variably hypodense tumor on T1 images because pf necrotic or intratumoral cystic areas, often with clearly demarcated paratumoral cyst(s) with no capsular enhancement (Figs. 16.1–16.3). It is of the utmost importance to detect even the smallest HB nodules, because they maintain cysts and may be the origin of later recurrences if left unnoticed. MRI may suggest high vascularity with tortuous feeding arteries and draining veins. In some cases, digital subtraction angiography (DSA) is indicated to demonstrate the vascularity and true nature of the lesions, or to demonstrate the smallest HB nodules. Diagnostic DSA might be followed by endovascular embolization to reduce the vascularity of the solid part; this, however, requires careful weighing of possible surgical gains against embolization hazards [3].

16.5.4 Diagnosis of Hemangioblastoma of the Retina

Mature HBs of the retina, resembling "sugar-powdered" raspberries, with adjoining dilated, tortuous arterioles and venules (feeder vessels), are distinctive enough to permit visual diagnosis after pupillary dilatation with indirect ophthalmoscopy, Goldmann 3-mirror contact lens, or non-contact lens fundus examination [13, 19]. Fluorescein angiography (FA) shows arteriovenous shunt with leakage of dye due to incompetent capillary walls. Incipient HBs are small, reddish or grayish dots without abnormal adjoining vessels, and incipient lesions may fail to fill with fluorescein. In the differential diagnosis, HBs of the optic disc may resemble papillitis, papilledema, chorioiditis, or chorioidal hemangioma. Cavernous hemangiomas of the retina appear as grape-like clusters of dilated vascular sacs without pronounced alteration in the adjacent arterioles and venules. Coats disease with dilated, tortuous, and leaking retinal venules may cause exudative detachment of the retina in children and teenagers.

16.5.5 Diagnosis of Von Hippel–Lindau Disease

A patient with HB of the CNS or retina is classified as having VHL if he or she has a germline mutation of the VHL gene, family history of VHL, or other VHL-related lesions [1]. Diagnosis of VHL is based on the VHL gene mutation analysis, with a nearly 100% detection rate in affected individuals, and/or the demonstration of clinical manifestation during long-term follow-up. Mutations in the VHL gene prevent its expression (deletions, frameshifts, nonsense mutations, splice site mutations) or lead to abnormal protein (missense mutations). Mutations are heterogeneous in type and position, and spread over the three exons. VHL shows intrafamilial and interfamilial differences in phenotype. It is not possible to reliably predict the severity and spectrum of VHL manifestations based on any single VHL gene defect.

16.6 Staging and Classification

Hemangioblastoma (HB) is a benign (WHO grade I), highly vascular, well-demarcated, slowly growing, solid or cystic neoplasm of unspecified cellular origin. It is confined to the CNS, the brain, spinal cord, and retina. In most cases, complete microsurgical removal of the HB nodule proves curative [1, 7, 11, 15, 18]. HB of the retina is histologically identical to HB elsewhere in the CNS [1]. In most cases, laser coagulation or cryocoagulation of the lesion is curative and prevents deterioration of vision [14, 19]. Some 25% of HBs (up to 50% of retinal HBs) may be associated with von

Hippel–Lindau disease (VHL), a rare autosomal dominant tumor syndrome. VHL predisposes to multiple tumors at an early age, most importantly HBs of the CNS and retina, bilateral RCCs, pheochromocytomas, and pancreatic tumors. VHL clearly reduces the length of life, with a mean age of 40–50 years at death, which is mainly caused by RCCs and HBs of the CNS.

16.7 Treatment

16.7.1 Synopsis

Sporadic HB in the retina and elsewhere in the CNS is a benign tumor that is in most cases curable at low morbidity with excellent preservation of function. VHL-associated HBs are often multiple and recurrent, defying established modes of therapy.

16.7.2 Microsurgery of Hemangioblastoma

Under the operation microscope, HB is a solid, well-circumscribed, highly vascular, red tumor, a nodule in the wall of a cyst, or a solitary tumor, embedded more or less in the cerebellum, brain stem, or spinal cord [1, 7, 11, 15, 18]. Microsurgery is the treatment of choice, aiming at seemingly complete removal of the HB nodule. Subtotal removals and mere biopsies should be avoided at all costs. The solid part should be removed in one piece with circumferential coagulation of the feeders. This also suffices to eradicate adjoining cyst(s), indicating that they are maintained by the solid part by mechanisms thus far unknown and not by a secreting capsule. In large or huge HBs of the cerebellum, the brain stem, or the spinal cord, the utmost microsurgical skill and delicacy in bleeding control and atraumatic dissection between the HB surface and the adjacent gliotic neural tissue are required. Preoperative endovascular embolization of feeders, helpful in selected cases by reducing vascularity, has lost its appeal because of the risks involved [3]. HB is microsurgically curable, but the risk of late recurrences may be higher than generally expected [15].

16.7.3 Stereotactic Radiotherapy of Hemangioblastoma

Stereotactic radiotherapy, given in one session as radiosurgery (SRS) with the gamma knife or the stereotactic linear accelerator with a micromultileaf collimator, would seem an ideal therapy as HBs are well-delineated, highly vascular, usually small and rounded, and in VHL patients often multiple or recurrent, defying repeated microsurgery [2, 7, 10, 11, 15, 18]. According to the present literature, small and medium-sized HBs react favorably to SRS with a margin dose of 18 Gy, with fewer responses at lower doses but more volume-dependent radiation-induced brain edema and injury at higher doses [17]. Similar to other solid tumors of WHO grade I, such as meningiomas and schwannomas, HBs tend to respond to SRS by slow volume reduction, but hardly become extinct. Also fractionated stereotactic radiotherapy (SRT) by linear accelerator in 1.8–2.0-Gy daily doses to a total of 50–56 Gy has been reported [9]. The slow response to SRS or SRT in the solid HB tissue may not suffice to prevent the adjoining cysts from enlarging, and, consequently, both the cyst and the solid part require long-term MRI follow-up.

16.7.4 Treatment of Hemangioblastoma of the Retina

Retinal HBs should be treated with laser or cryocoagulation when small or even asymptomatic for better prognosis of vision and lower risk of complications [1, 14, 19]. In HBs of the papillary or macular area, however, coagulation may cause a central visual field defect, and it is not advised until exudation develops. Laser coagulation often requires multiple sessions to scar the entire HB. At 2 months, attenuation of feeders and absence of fluorescein leakage from the HB suggest a good result. Scatter laser treatment is frequently given to the retina surrounding the capillary hemangioma in an effort to prevent post-treatment extension of any exudative retinal detachment. The laser treatment is particularly effective against tumors that are up to 3 mm in diameter. In cryocoagulation of larger lesions (>3 mm in diameter), the cryoprobe is located over the HB transsclerally in indirect ophthalmoscopy. If the feeders have not attenuated by 2 months, cryotherapy should be repeated. At 6

months, the HB should appear as a pigmented scar, with surrounding exudate diminished or having disappeared, feeders atrophic, and the macula dry. Brachytherapy with episcleral isotope plaques has also been used to treat large lesions. Late recurrences may develop due to incomplete primary destruction, but in VHL new tumors may be mistaken for recurrences. In VHL, the appearance of new, multiple, and bilateral HBs of the retina may threaten vision. Retinal detachment without vitreous traction may be treated by extraocular scleral buckling procedures. Macular preretinal fibrosis, vitreous hemorrhage, or retinal detachment threatening the macula may necessitate intraocular vitreoretinal surgery. Cataract and neovascular glaucoma following total retinal detachment are late complications with a poor prognosis. Finally, enucleation may become mandatory in the case of a blind and painful eye.

16.7.5 Treatment of Hemangioblastomas in VHL

In VHL, microsurgical treatment of multiple HBs often fails in the long run [2]. Removed tumors tend to recur, and new ones develop; some are symptomatic, others incidental [2, 7, 11, 15, 18]. It is often difficult to decide which tumors should be removed, and operative risks should be weighed against the natural course. The gold standard is to treat only tumors that are symptomatic or clearly growing. In VHL, more often than in sporadic cases, HBs are located in the brain stem and spinal cord [11, 18], increasing the risk of operative morbidity and mortality. Stereotactic radiotherapy is an option to treat HBs in eloquent areas, but overlapping fields in multiple HBs increase the risk of radiation injury in the adjacent brain [9, 17].

16.7.6 Chemotherapy of Hemangioblastoma

So far, there is no proven drug therapy against HB tissue. Increasing data on the signaling cascades related to the VHL gene [8] have raised interest in novel growth factor or tyrosine kinase-modulating drugs in the experimental treatment of advanced RCC [4] as well as in HBs that defy established modes of therapy.

16.8 Prognosis/Quality of Life

16.8.1 Hemangioblastoma

Sporadic hemangioblastoma is a microsurgically curable benign tumor [1, 15]. The operative morbidity and mortality for classic cerebellar cystic tumors is very low. Operative risks increase for spinal HBs and, in particular, for large solid lesions in the brain stem [11, 18]. Stereotactic radiotherapy appears to be a valuable method to control but not ablate HBs in selected cases [9, 17].

16.8.2 Hemangioblastoma of the Retina

Hemangioblastoma of the retina, if truly sporadic, as some 50% may be, can be ablated safely in most cases with permanent sparing of the vision in the eye.

16.8.3 Von Hippel–Lindau Disease

VHL is a deadly disease affecting young patients of child-bearing age. RCC develops in about 40% of VHL patients and has become the leading cause of death due to advances in the treatment of HB of the CNS. Multiple and recurrent HBs – as well as ill-balanced efforts to treat them – may cause devastating morbidity. In patients with bilateral RCCs, decisions have to be made between nephron-sparing surgery [16], renal ablation, dialysis, and even renal transplantation.

16.9 Follow-Up/Specific Problems and Measures

16.9.1 Hemangioblastoma

Patients with HB should undergo general exclusion of VHL by the following examinations: family history; contrast-enhanced MRI of the brain, the spinal cord, and the organs of the abdominal cavity; retinal microscopy by an ophthalmologist. Mutation analysis may also be considered. In the long run, recurrences after

completely removed lesions may appear at an undefined risk. In the Helsinki series, with the primary operation taking place between 1953 and 1993, 9 of 74 apparently non-VHL patients developed a local recurrence at a median of 11 years (range 3–35) [10].

16.9.2 Hemangioblastoma of the Retina

In HBs of the retina, it is even more crucial than in HBs elsewhere in the CNS to achieve early diagnosis and pursue definitive ablative treatment in the early phase – to preserve vision as well as to exclude the presence of VHL.

16.9.3 Von Hippel–Lindau Disease

Patients with VHL should be evaluated and monitored yearly by a dedicated VHL team, composed of a coordinator specialized in VHL who consults and works together with a neurosurgeon, an ophthalmologist, a nephrologist, a urologist, or an endocrinologist, and others, depending on the patient's phenotype. VHL patients and families should be offered genetic counseling and mutation analysis. The VHL Family Alliance, active in several countries, plays an important role by providing established data on VHL as well as upgrades of novel therapies on their web pages (www.vhl.org).

16.10 Future Perspectives

16.10.1 Novel Drug Therapies for Hemangioblastoma

Many VHL patients with HBs and some sporadic HB patients would benefit from novel effective modes of systemic drug therapy against HBs. In VHL, HBs are often multiple and recurrent, in eloquent areas with increased risks associated with microsurgery and stereotactic radiotherapy. An ideal therapy would abolish the existing HBs and prevent the appearance of new ones, but tumor shrinkage or stable disease for years would also be satisfactory if the treatment were well tolerated. HBs of the CNS and the retina could be targets for "antiangiogenic therapy" as they are highly vascular and express a number of growth factor receptors [1]. In addition, HB is receiving scientific attention because of the association with the mutated biology of *VHL* and pVHL [8]. However, the emerging view from early studies using interferon [14] or small molecules is that some reduced vascularity or tumor stability, but no tumor eradication or remarkable regression could be achieved – at least by single-agent approaches. Another line of research and drug development, apart from the *VHL* and pVHL biology, would be to elucidate the origin and qualities of the precursor cell for the HB stromal cell that confines HBs to the CNS and, in particular, to the retina [1]. So far, no proven drug therapy against HB has been presented.

16.10.2 Novel Drug Therapies of Renal Cell Carcinoma

The need for novel therapies is even more urgent in RCC as the leading cause of death in VHL, as well as in advanced sporadic RCC, which is 50 times more frequent than VHL-associated RCC [4].

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